are nevertheless regarded as a highly characteristic feature of the rheumatoid joint and their appearance in our experimental lesions is therefore all the more noteworthy. The significance of this follicular response is by no means clear but its resemblance to the lymphoid follicles in a lymph node draining an area of antigen injection suggests that it is in some way associated with the immune response. This inference is supported by the associated infiltration of plasma cells, cells now well recognized as producers of immune globulin. The similar appearance of the thyroid gland in Hashimoto's thyroiditis, a condition in which an immune response to thyroid antigens is well established, confirms the view that this type of reaction may be taken as evidence of some locally persistent antigen.

If this interpretation of the lymphofollicular and plasma cell response is correct, it implies the persistence of the antigenic stimulus for months after the single intra-articular injection of fibrin. This could arise in two ways: either from some interference with the mechanism that is normally capable of removing fibrin from the joint with remarkable speed and efficiency, or because of constant renewal of antigen. Some evidence exists for both these possibilities. We have recently shown (Dumonde & Glynn 1965, unpublished observations) that even in guinea-pigs, which normally possess an extremely active fibrinolytic system capable of disposing in a few days of fragments of fibrin up to 100 mg wet weight, human fibrin may persist for over sixteen weeks in pre-immunized animals. This suggests that immunity to a foreign antigen may seriously interfere with its removal, at least in the solid state, and such interference can be sufficient in degree to account for the observed persistence of activity of our experimental arthritis. Evidence for the constant renewal of antigen is less convincing, but is suggested by the observation to which I have already referred, that in a significant proportion of rabbits immunized with either human or their own fibrin, reactions of delayed hypersensitivity can be obtained to their own fibrin, i.e. a state of auto-immunity has been induced to an inflammatory product, namely, fibrin. This could then result in the establishment of a vicious circle in which inflammation leads to local fibrin formation and this in turn, by virtue of the autoimmune state, leads to further inflammation. It should, of course, be emphasized that these two processes are not mutually exclusive and each could contribute to the observed persistence of the experimental lesion. Furthermore, although in the experiments here described I have confined myself to those in which the antigen was fibrin, there is no reason to believe that similar results could not be achieved using other inflammatory products as antigen. Our current experiments do indeed show that similar results can be obtained (Kaklamanis, Phillips & Glynn 1965, unpublished observations).

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Avascular Necrosis of the Femoral Head in the Dog

Avascular necrosis of the femoral head in the dog has been recognized for some years (Formston & Knight 1942, Frost 1959). It bears certain similarities to Perthe's disease in man, and it has been shown that the ætiology of Perthe's disease is, in part, genetic (Stephens & Kerby 1946). Avascular necrosis of the femoral head in the dog therefore makes a good subject for comparative study.

Clinical Features

During the last three years one of us (J H) has examined 20 cases, some details of which are given in Table 1. With one exception all the cases were unilateral and the onset of symptoms occurred between 4 and 12 months of age. This is comparable with the age incidence of Perthe's disease.

The stages of the disease also are comparable with those seen in man: onset of pain followed by varying degrees of destruction and resorption of the femoral head and, finally, regeneration with a return to normal bone and cartilage. The femoral head is deformed which results in joint dysfunction and in time to an osteoarthritis.

This disease is only seen in certain of the smaller breeds and is especially common in working terriers and miniature poodles. In the experience of one of us (J H) it does not occur in

Table 1
Breed, sex distribution, laterality, and radiological types of avascular necrosis of the femoral head

	Breed		
	Poodle	*Terrier*	*Spaniel*
Male	4	2	0
Female	6	7	1
Total	10	9	1
Right hip	2	2	1
Left hip	8	5	0
Radiological group:			
1	4	0	1
2	0	3	0
3	3	5	0
4	3	1	0

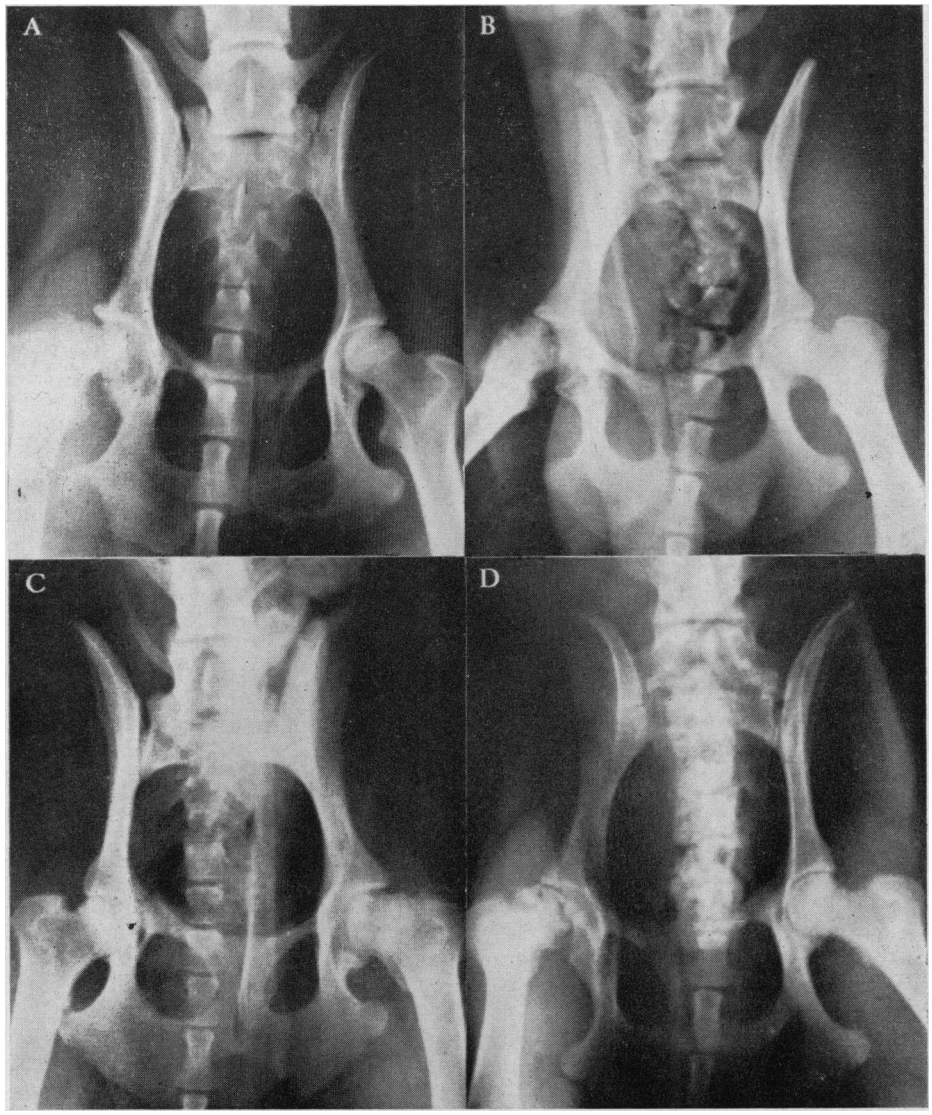

Fig 1 *Radiological types of avascular necrosis of the femoral head in the dog (for explanation* see *text)*

the corgi or dachshund nor in any of the large breeds such as the Alsatian, Labrador and boxer.

Radiological Aspects

The radiological manifestations vary considerably and can be classified into four main categories:

Group 1: Complete breakdown of the dorsal surface of the femoral head (Fig 1A).

Group 2: Localized areas of necrosis which may or may not break through the articular surface (Fig 1B).

Group 3: Diffuse lesion with expansion of the femoral head and neck. Articular surface remains intact (Fig 1C).

Group 4: Lesion originates at the epiphyseal plate and may extend to a complete disintegration of the epiphysis (Fig 1D).

Genetic Analysis

The ætiology of the disease is obscure. Trauma, nutritional factors, infection, endocrine and vascular disturbances have all been implicated, but the incidence distribution indicates that a hereditary factor is present. The disease is found preferentially in certain breeds of dog, notably in miniature poodles and in working terriers (Table 1). There is no demonstrable difference between breeds in sex distribution or laterality. There are

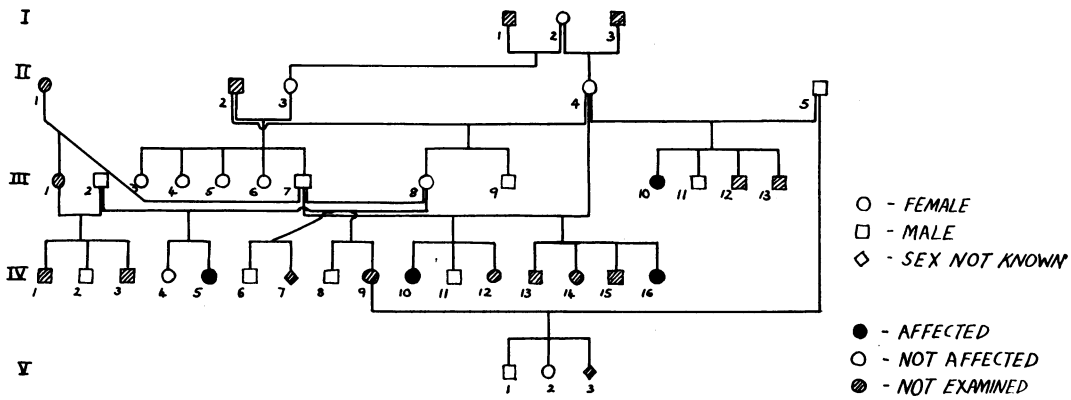

Fig 2 *Pedigree of poodle kindred with some animals suffering from avascular necrosis of the femoral head*

not sufficient data to enable a test of significance to be made between breeds in the relative occurrence of different radiological types. However, it is notable that 4 out of 10 poodles have lesions on the dorsal surface of the head of femur whereas none of the 8 terriers shows such lesions. This suggests a breed difference.

Four of the miniature poodles that had avascular necrosis were in the same kindred (Fig 2). All the affected animals are bitches but this does not necessarily reflect a significant sex difference since there are few male animals in the affected sibships. The remarkable feature of the pedigree is that one animal (II.4) is a recent ancestor of the four affected animals, being the mother of three of them and the grandmother of the fourth. If the mode of inheritance is through an autosomal dominant gene then it has failed to manifest itself in II.4 and in either III.2 or, more probably, III.8. If an autosomal recessive gene is concerned it must have been introduced into the kindred three times through I.2, II.5 and III.2; this is unlikely. Unless there is a genuine sex limitation in this kindred, sex linkage can be ruled out. The simplest hypothesis is that the mode of inheritance is that of an autosomal dominant of limited penetrance. The gene might have originated by mutation in II.4 or have been introduced into the kindred by I.2 or I.3. The gene is not manifest in II.4 who must have possessed it. Eleven of the descendants of II.4 have been examined, each of which had a 0·5 probability of acquiring the gene. Four of these animals show the condition as against the expectation of 5·5 on the hypothesis of an autosomal dominant. If the figures are corrected to allow for the bias due to the ascertainment of the pedigree through a propositus, the incidence is 3 out of 10. The data are too few for meaningful statistical evaluation but the facts are consistent with the hypothesis of an autosomal dominant of limited penetrance.

The concept of limitation in penetrance implies that several genes are acting. It is sufficiently flexible to allow an explanation of many diverse pedigrees. The hypothesis must therefore be regarded with caution and as an indicator for further work rather than as an answer. It is in the planning of this future work that the advantage of working with dogs becomes apparent. We have 3 of the affected animals, III.10, IV.10 and IV.16. Using these we can make defined crosses. The purpose of the breeding programme is twofold: one is to produce a sufficient stock of affected animals to allow experimental and pathological studies of the development of the condition, and the other is to gain further genetic information. We have as yet found no affected dog available to use for mating with the affected bitches, nor a dog of which we can be confident that it is not carrying the gene. It must be emphasized that to clear a kindred of carrying the gene and hence to be confident that a particular individual is not carrying it, requires as much work as has been done on the kindred we have described. We have tried mating one of the affected bitches to its unaffected litter mate. This type of mating has a reasonable chance of producing affected offspring but is unsatisfactory because the genotype of the dog is very uncertain. The mating between IV.10 and IV.11 yielded offspring but they died young. However, we intend to persist with the breeding programme using the unaffected sibs which are available to us.

Treatment

The method adopted is indicated by the pain. If the pain subsides and the dog commences to use its leg within two to three months a satisfactory functioning joint can be expected. Inevitably an osteoarthritis will develop but its onset and rate of development will depend on the degree of distortion of the femoral head. If after three months

pain is still present and the dog continues to carry its leg, amputation of the femoral head is recommended. This results in an immediate and dramatic freedom from pain. Whether an arthroplasty is performed or a femoral head prosthesis fitted is a matter of choice but in small dogs the former procedure leaves little to be desired.

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Arthropathy in Pigs

The principal bacteria associated with arthritis in pigs are *Erysipelothrix insidiosa*, streptococci and hæmophilus. The course of erysipelas is well documented (Collins & Goldie 1940). Vaccination is widely practised and protects against the acute form of the disease, although it may sensitize the pig to the chronic, arthritic form (Freeman & Berman 1964). As *E. insidiosa* is almost ubiquitous, and as arthritis due to hypersensitivity to it can occur without organisms being demonstrable in the lesions, it is possible to postulate that most arthropathy in pigs stems from the organism (Duthie & Lancaster 1964). Grabell *et al.* (1962) have made a study of discospondylitis due to erysipelothrix.

More spectacular arthritis resembling Glässers disease has been described associated with a PPLO and hæmophilus (Lecce 1960) and with *Mycoplasma hyorhinis* (Roberts *et al.* 1963). Classical joint ill and navel ill associated with pyogenic bacteria also occur in pigs.

I do not believe that all arthropathy in pigs arises from an infectious cause. Sabec (1960) has described a tarsitis of pigs, which probably has a non-infectious ætiology, and it is probable that a large proportion of other joint lesions occur in the absence of infectious agents. It is, in fact, quite difficult to find a pig over the weight of 75 kg that does not have some arthritic condition. To understand this it is necessary to know the background to modern pig husbandry.

Few pigs live to a ripe old age, so that senile changes are not a problem. Some 95% of all pigs reared in this country are killed at either 4 or 7 months for the pork or bacon markets. They are, of course, kept for profit, and variations in production cost of a penny per pound live weight can halve this profit. A higher price is paid for pigs which produce the sort of joints that the bacon factory prefers – the so-called 'desirable carcase characteristics'. In intensive units it is also preferable that the pigs should grow rapidly so that

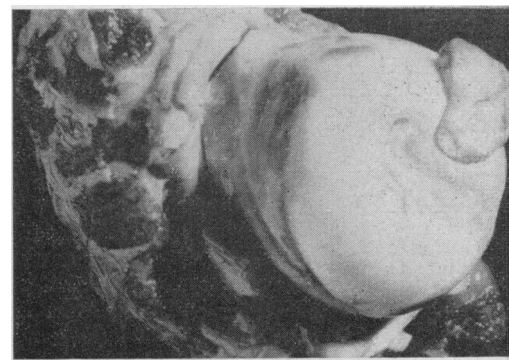

Fig 1 *Wear lesions in the femoral head*

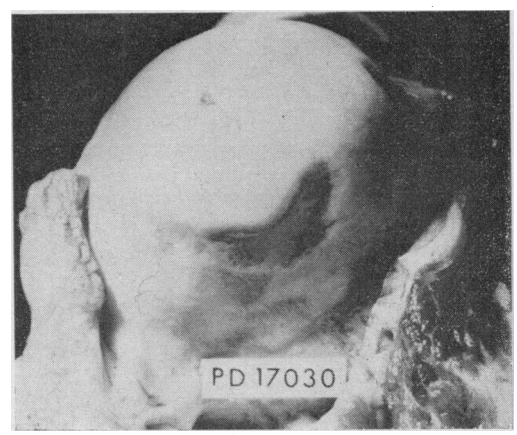

Fig 2 *Wear lesions in the humeral head*

there can be a quick turnover. For the last twenty-five years, or 15 generations, therefore, pig breeding has been intensively channelled towards producing a pig with the right carcase characteristics which grows rapidly and converts food efficiently. Little attention has been paid to the pigs' mobility.

Three types of lesion occur in the articular cartilage, and these may be called 'wear lesions', 'proliferation lesions' and 'lift lesions'. Wear lesions occur principally and earliest on the femoral and humeral heads (Figs 1 and 2). In the early lesion the cartilage in affected areas becomes thin but, until it is worn through and eburnation occurs, there is no reaction in the underlying bone. Proliferation lesions occur mostly on the humeral head and distal femur (Fig 3), and in this case there is collapse of the underlying bone and the formation of 'brood capsules' in the cartilage. Lift lesions (Fig 4) occur principally in the ulnar notch, and here the cartilage becomes detached from the bone, the primary fault probably occurring in the ossifying calcified cartilage just beneath the articular surface.